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Exosomes produced from cancer cells' genomic and proteomic composition

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ABSTRACT

Exosomes produced by tumours (called tumor-derived exosomes, or TDEs) are involved in the initiation and development of several cancerous processes, such as tumour microenvironment (TME) remodelling, angiogenesis, invasion, metastasis, and drug resistance. Exosomes deliver diverse payloads to destination cells, where they activate or inhibit multiple signalling pathways. We go through exosome biosynthesis, exosome-mediated metastasis, and chemoresistance in this review. The involvement of tumor-derived exosomes in angiogenesis and the remodelling of the tumour microenvironment are also discussed. Additionally, epithelial mesenchymal transition (EMT) exosome induction is underlined. More significantly, we go into great detail on how exosomes control treatment resistance in various malignancies. In order to develop new therapeutic approaches for cancer progression, particularly to overcome therapy-resistance and prevent metastasis as major factors of cancer mortality, it may be helpful to understand exosome biogenesis, their contents, and the molecular mechanisms and signalling pathways that are responsible for metastasis and drug-resistance mediated by TDEs.

Keywords: Exosomes; Drug-resistance; Cancer progression; Metastasis; Multivesicular bodies

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INTRODUCTION

Exosomes are membrane vesicles that are secreted, and they have been suggested as a useful tool for diagnosing many disease conditions, including cancer. Exosomes' characteristics, such as their stability in bodily fluids, enable their effective isolation and make them the perfect tool for research on the early identification and assessment of illness. In recent years, a lot of information about the messenger RNA, microRNA, and protein contents of exosomes has been gathered. The functional role that exosomes play in the onset and course of illness has also been extensively studied. It has been demonstrated that tumour cells release exosomes, frequently in greater quantities than normal cells, and that these exosomes might contain the genomic and proteomic markers exclusive to the tumour cells from which they originated. Exosomes from cancer cells have been demonstrated to have a functional role in the course of the disease, and although these distinctive characteristics make exosomes suitable for cancer diagnosis. Here, we examine the distinctive genomic and proteomic compositions of exosomes derived from cancer cells as well as their functional contributions to the advancement of tumours. Exosomes are tiny membrane vesicles with a size range of 40 to 100 nm that develop inside multivesicular bodies (MVB) and are released once the MVB fuses with the plasma membrane. Exosomes were initially discovered in 1987 when Johnstone discovered that vesicles released from monolayer cells in culture still had part of their parent cells' enzymatic activity. Exosomes were eventually shown to be the remains of the endocytic process following endosomal sorting of constituents that are not lysosomally destroyed. Exosomes are then formed from these vesicles and discharged from the cell. Exosomes were first considered a means of getting rid of extra membrane proteins, particularly during reticulocyte development. The current understanding is that exosomes can play important biological roles and that this is not always the case. It is important to note that there is some ambiguity around the phrases "exosome" and "microvesicle." Most studies distinguish between the two mostly based on sizes, with exosomes being between 40 and 100 nm and microvesicles being between 100 and 200 nm. While some of the research referenced in this review utilise these words in more precise ways, others do so without distinction. Others just use the word "microvesicle" to refer to both kinds of secreted vesicles. Since the study of exosomes and microvesicles is still in its infancy, these categories could develop throughout time to become more exact or might

incorporate other criteria to categorise different kinds of vesicles. Cholesterol, sphingomyelin, and ceramide, as well as proteins connected to lipid rafts, are abundant in exosome membranes. Exosomes are very stable due to their components, and as a result, they may be extracted from a variety of biological fluids, including blood, urine, breast milk, ascites, and saliva. Exosomes may be easily extracted from these fluids once they have been collected by utilising differential ultracentrifugation to first remove big cells and debris, and then pellet the exosomes. Exosomes are perfect for use in diagnostic biomarker investigations because they are so common in biological fluids. Exosomes may potentially have a useful purpose in human biology, according to research[1-5].

Intercellular communication is essential for cells to adjust to a variety of intra- and extracellular modifications happening in many processes, including embryonic development, response to damage, homeostasis, and other activities. Different methods of cell-cell communication, including close physical touch and remote interactions through circulation and bodily fluids, are employed to relay different messages. A particular and highly controlled transport process is the transfer of biological mediators via exosomes and microparticles.

Numerous studies have shown that exosome-mediated factors can influence cancer cell interactions inside the TME to facilitate tumour genesis, metastasis, and therapeutic resistance. Various cells, including fibroblasts, endothelium, and immunological cells, as well as a variety of extracellular matrix elements, such as cytokines, growth factors, and exosomes, make up a proper niche. The survival and growth of cancer stem cells (CSCs) and other tumour cells can result from niche creation, which can cause a malignancy[6]. The cancer stem cell theory postulates that CSCs, a subset of tumour cells, are in charge of the upkeep and recurrence of tumours. Numerous studies have shown that CSCs are crucial in the tumours' resistance to radiation and chemotherapy. Numerous studies showing how the tumour microenvironment (TME) may alter the tumour cells' malignant behaviour have highlighted the crucial function of the TME in altering tumour behaviour[7]. The role of exosomes on many tumorigenic pathways in TME, including stemness, angiogenesis, metastasis, and hypoxia-induced EMT, has been shown. Furthermore, according to previous research, removing exosomes from the bloodstream slows the growth of tumours. A functional change in the tumour microenvironment via various interacting mediators, such as exosomes, is also predicated on the onset of carcinogenesis. These mediators include sufficient mutations to obtain malignant potential. Many researches are very interested in the biological functions of TDEs as the microvesicles in bodily fluids in the development of TME. In order to create new and more successful treatment plans, it is crucial to understand the molecular processes and signalling pathways controlled by exosomes that encourage cancer cell metastasis and medication resistance[8-10].

CONCLUSION

We discussed exosome formation and the primary pathways for exosome-mediated metastasis and chemoresistance in this review. Designing new therapies that target exosome-mediated carcinogenesis, metastasis, and chemoresistance will be made easier by understanding the molecular processes behind exosome biogenesis, metastasis, and chemoresistance. Exosomes are adaptable and important intercellular connectors that transmit biomolecules via a controlled manner. Exosomes serve several functions and exhibit organotropic behaviour, therefore a deviation from this function gives tumours a useful tool. Exosomes produced by tumours aid in the development of the pre-metastatic niche, angiogenesis, invasion, and therapeutic resistance of the tumour cells. There has been a push in research to use exosomes as a therapy method by loading them with therapeutic agents such functional proteins, miRNAs, and different chemotherapeutics since exosomes are implicated in many pathophysiological disorders. Exosome-based therapeutic techniques for cancer therapy still have a long way to go until the obstacles that now stand in their way are removed. However, a number of important features of the molecular underpinnings of metastasis and resistance, distant cell contacts, exosome heterogeneity, and exosome-mediated crosstalk in tumour microenvironment, have come to light. Our understanding of exosomal-mediated therapy-resistance in various cancers will be guided by designing various research approaches in this new, vast area of study based on the tumour context, and the application of these findings to the clinical setting will provide a cutting-edge and efficient treatment option for future cancer patients.

Exosomes produced by parent cells are reflective of their parent cells, and tumor-derived exosomes can reveal a lot about the tumour cells that gave rise to them. Tumor-derived exosomes can contribute significantly to the course of illness. If non-invasive, early detection techniques are to be created, studying tumor-derived exosomes is essential. Although there are many errors in the present detection techniques, it is probable that exosome-based detection will also have some errors. Cancer cells are well known for creating mutations and altering protein expression levels to boost cell survival and evade conventional therapies. Exosome markers utilised in a cancer detection screen must thus nearly exclusively be expressed in exosomes originating from tumours. The exchange of information on the genomes and proteomics of exosomes has been made easier by databases like ExoCarta and the Urinary Exosome Protein Database. It will be crucial to identify the variables that are most pertinent to exosome functions as we continue to gather this data. In the majority of the examples discussed below, the authors have noticed that the addition of tumor-derived exosomes to normal cells may result in widespread effects, such as angiogenesis or cell proliferation. However, a single protein or RNA molecule seldom accounts for these effects. Future exosome research should concentrate on identifying the "non-reducible units" needed for these tasks.

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